

REMARKS

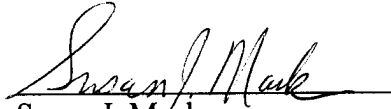
Applicants provide herewith * 7) (a summary of a presentation at a scientific meeting) which was not available at the time of filing our Response dated September 17, 2008.

Disease	HGF	VEGF
acute pneumonia	1) <i>J Biol Chem</i> , 268 , 21212 (1993) 2) <i>Am J Physiol</i> , 270 , 1031 (1996) 3) <i>Am J Respir Crit Care Med</i> , 162 , 707 (2000) 4) <i>Am J Pathol</i> , 155 , 949 (1999) 5) <i>Am J Respir Crit Care Med</i> , 158 , 386 (1998) 6) <i>Am J Physiol</i> , 278 , L382 (2000)	*7) Vascular endothelial growth factor (VEGF) is protective against acute lung injury ; Koh Hidefumi, Ishizaka Akitoshi, et al: ATS International Conference, Atlanta, Georgia, U.S.A ; 2002/05 8) <i>Eur Respir J</i> , 18 , 100 (2001)
pulmonary fibrosis	9) <i>Am J Respir Crit Care Med</i> , 156 , 1937 (1997) 10) <i>Respir Med</i> , 91 , 511 (1997) 11) <i>Respir Med</i> , 92 , 273 (1998) 12) <i>Am J Respir Cell Mol Biol</i> , 16 , 388 (1997)	13) <i>Am J Respir Crit Care Med</i> , 166 , 382 (2002.8)
pulmonary hypertension	14) <i>Circulation</i> , 106 (suppl I), I-264 (2002)	15) <i>Circulation</i> , 104 , 2242 (2001) 16) <i>Am J Respir Cell Mol Biol</i> , 23 , 762 (2000) 17) <i>FASEB J</i> , 15 , 427 (2001)
COPD	18) <i>Am J Respir Cell Mol Biol</i> , 26 , 525 (2002.5) 19) <i>Development</i> , 125 , 1315 (1998) 20) <i>Am J Respir Crit Care Med</i> , 160 , S72 (1999)	21) <i>Am J Respir Crit Care Med</i> , 163 , 737 (2001)
asthma	22) Japanese Journal of Allergology, 47 , 980 (1998) 23) <i>Am J Respir Crit Care Med</i> , 156 , 591 (1997)	

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,


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Date: October 8, 2008

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23.7±1.4*

*P<.05 vs

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normal human lung (Kaner KJ et al., *Mol Med* 2001) and recent work suggests that pulmonary VEGF may be important in recovery from ARDS (Thickett DR et al., *AJRCCM* 2002). We have previously shown that the functional +936C/T VEGF polymorphism is associated with both susceptibility to and severity of ARDS (Medford ARL et al., *ERJ* 2002 (abstract)). We have investigated the relationship between plasma and bronchoalveolar lavage (BAL) VEGF levels and +936 genotype in ARDS. **METHODS:** Blood and BAL samples were obtained from ventilated at risk and ARDS subjects. Blood samples were genotyped as described previously (Medford ARL et al., *AJRCCM* 2002 (abstract)). VEGF levels in BAL and plasma were determined by ELISA. **RESULTS:** In at risk subjects, the CT and TT genotypes were associated with a lower plasma VEGF level (129.1 pg/ml versus 304.7 pg/ml, $p = 0.04$) and a trend towards lower BAL VEGF level (4754 pg/ml versus 11658 pg/ml, $p > 0.05$). However, in the ARDS subjects, there was no relationship between genotype and plasma or BAL levels. **CONCLUSIONS:** The +936 C/T VEGF polymorphism is related to reduced plasma VEGF levels in at risk but not ARDS subjects; no absolute relationship is evident between the polymorphism and BAL VEGF levels in either at risk or ARDS subjects.

This Abstract is Funded by: Myre Sim Fund Grant

Vascular Endothelial Growth Factor (VEGF) Is Protective Against Acute Lung Injury

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VEGF was recently found to be a major survival factor for endothelial cells although it had initially been reported as a vascular-permeability-increasing cytokine. We previously reported that epithelial lining fluid (ELF)-VEGF concentrations of survived ARDS patients (6690 ± 577 pg/ml; mean \pm SEM) were significantly higher than those of the deceased patients (4579 ± 862 , $p < 0.05$) and the control subjects (2869 ± 487 , $p < 0.001$). Negative correlation was observed between ELF-VEGF concentration and lung injury score ($p < 0.01$). We also showed that 125I-albumin permeability was attenuated by pretreatment of VEGF in a mouse model of endotoxin (LPS)-induced acute lung injury. In this study we investigated effects of VEGF, in vitro, on permeability, apoptosis and induction of p53, Bax, Caspase using human pulmonary artery endothelial cell monolayer (HPAEC). LPS increased HPAEC permeability, whereas VEGF did not have any effects on the permeability. Pre-incubation with VEGF attenuated the increase in HPAEC permeability induced by LPS ($p < 0.05$). Although LPS enhanced the number of apoptotic cells ($p < 0.05$), this was distinctly inhibited by pre-incubation with VEGF ($p < 0.05$). In addition, VEGF significantly decreased the induction of p53, Bax and caspase activity in HPAEC upon LPS stimulation. These results suggest that VEGF may be protective against LPS-induced acute lung injury by preventing apoptosis process.

This Abstract is Funded by: a grant-in-aid for Fundamental Scientific Research from the Education Ministry of Japan 07670678 (A. I.).

The Effect of Large Volume Packed Red Blood Cell Transfusions on Standard Blood Genotyping Techniques

J.J. Hine¹, D.H. Strong¹, A.M. Zelazoski¹, U. Broeckel², J.P. Maloney¹. ¹Division of Pulmonary and Critical Care Medicine; ²Human and Molecular Genetics Center at the Medical College of Wisconsin, Milwaukee, WI. Email: jjhine@aol.com

PURPOSE: The genomics of acute lung injury (ALI) is a rapidly growing field. Transfusion of large volumes of packed red blood cell (PRBC) is common in patients with ALI and creates a potential for spurious genotyping due to donor lymphocyte contamination. As PRBC units are relatively leukocyte poor, we hypothesized that large volume PRBC transfusions would not interfere with standard genotyping techniques. **METHODS:** We enrolled 11 patients (most with ALI) and obtained paired blood (donor contamination) and buccal swab (donor absent) specimens. Two of the 11 patients had received allogeneic bone marrow transplants (BMT) and were used as positive controls for discordance between buccal and blood genotypes. All non-BMT patients had received PRBC transfusions ranging

given a burn (4%
smoke (48 breaths)
Formula, 4 ml/kg
60 mg) was given
Conclusion: The
lung wet-to-dry
inhibited the inc
the lung injury
This Abstract

Effect of Colloid and Pulmonary

X. Su¹, C. Mathay³, R. University, S. University, S. CA. Email: s

The purpose was to evaluate the effect of colloid on the balance in a anesthetized dog group (n = 10). An iv injection of hemofiltrate continued for 24 hours. Compliance, edema, and output, oxygenated water was 3.5 protein corectory cells i (MV 35 \pm 10) in the HF improved proinflammatory beneficial a reduction This A

Inflammation Model of S.C.I

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